TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 1581/00240

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/762215

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/03574	2 June 2000	4 June 1999

TITLE OF INVENTION

Processes for the Preparation of 5-Hydroxy-3-Oxopentanoic Acid Derivatives

APPLICANT(S) FOR DO/EO/US

Nishiyama, Akira , Inoue, Kenji

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. § 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3).

9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☐ A translation of the Annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification

15. ☐ A change of power of attorney and/or address letter

16. ☒ Other items or information: International Search Report

U.S. APPLICATION NO (If known, see 37 CFR 1 5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/762215	PCT/JP00/03574	1581/00240

☒ The following fees are submitted:

	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO.....**$860.00** International preliminary examination fee paid to USPTO (37 CFR 1.482) ....**$690.00** No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))**$760.00** Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....**$1,000.00** International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$860**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$**	

Claims	Number Filed	Number Extra	Rate		
Total Claims	20- 20 =	0	X **$18.00**	**$**	
Independent Claims	3- 3 =	0	X **$80.00**	**$**	
Multiple dependent claim(s)(if applicable)			+ **$270.00**	**$**	
TOTAL OF ABOVE CALCULATIONS =				**$860**	
Reduction by 1/2 for filing by small entity, if applicable.				**$**	
SUBTOTAL =				**$860**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				**$**	
TOTAL NATIONAL FEE =				**$860**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				**$**	
TOTAL FEES ENCLOSED =				**$860**	
				Amount to be: refunded	**$**
				charged	**$**

a. ☒ A check in the amount of $860 to cover the above fees is enclosed.
b. ☐ Please charge my Deposit Account No. **22-0185** in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.
c. ☒ The Director is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **22-0185**. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status

SEND ALL CORRESPONDENCE TO:
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SIGNATURE
Burton A. Amernick
NAME
24,852
REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	
Akira Nishiyama et al.	:	
Serial No.: To be assigned	:	Art Unit: To be assigned
Filed: Herewith	:	Examiner: To be assigned
For: Processes for the Preparation of 5-Hydroxy-3-Oxopentanoic Acid Derivatives	:	Atty Docket: 1581/00240

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-captioned case as follows.

IN THE CLAIMS

Please amend the claims as follows.

Claim 3, line 1, delete "or 2".

Claim 4, line 1, delete "2 or 3".

Claim 8, line 1, delete "or 7".

Claim 9, line 1, delete "7 or 8".

Claim 12, line 1, delete "or 11".

Claim 13, line 1, delete "11 or 12".

Claim 14, line 1, delete "any of Claims 1 to 13" and insert ---Claim 1---.

Claim 15, line 1, delete "any of Claims 1 to 14" and insert ---Claim 1---.

Claim 16, line 1, delete "any of Claims 1 to 13" and insert ---Claim 1---.

Claim 17, line 1, delete "any of Claims 1 to 16" and insert ---Claim 1---.

Please add the following new claims.

18. The process according to Claim 2

wherein, referring to the acetic acid ester, R^1 represents a tert-butyl group.

19. The process according to Claim 2

wherein a magnesium halide is added in permitting the lithium amide to act.

20. The process according to Claim 3

wherein a magnesium halide is added in permitting the lithium amide to act.

REMARKS

The claims have been amended to eliminate multiple dependency and to improve their format. None of these amendments is believed to involve any new matter. Accordingly, it is respectfully requested that the foregoing amendments be entered, that the application as so amended receive an examination on the merits, and that the claims as now presented receive an early allowance.

Respectfully submitted,

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Telephone: 202-331-7111

Date: 2-05-01

SPECIFICATION

PROCESSES FOR THE PREPARATION OF 5-HYDROXY-3-OXOPENTANOIC ACID DERIVATIVES

TECHNICAL FIELD

The present invention relates to a process for producing a 5-hydroxy-3-oxopentanoic acid derivative which is of value as a pharmaceutical intermediate, particularly an intermediate of an HMG-CoA reductase inhibitor.

BACKGROUND ART

The hitherto-known process for producing a 5-hydroxy-3-oxopentanoic acid derivative includes the following processes.

(1) The process in which 3-hydroxypropionic acid imidazolide prepared from 3-hydroxypropionic acid and diimidazoyl ketone is coupled to a malonic acid monoester monomagnesium salt (Synthesis, 1992, 4, 403-408).

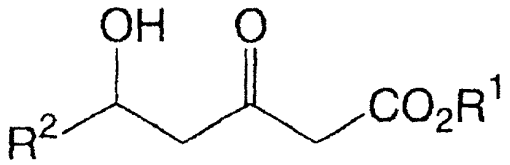
(2) The process in which a lithium enolate prepared from tert-butyl acetate and lithium diisopropylamide is reacted with a 3-hydroxypropionic acid ester (Japanese Kokai Publication Hei-8-198832, Chem. Pharm. Bull., 1994, 42 (11), 2403-2405, Tetrahedron Lett., 1993, 49 (10), 1997-2010, Tetrahedron, 1990, 46 (29), 7283-7288, Tetrahedron Asymmetry, 1990, 1 (5), 307-310, Tetrahedron Lett., 1989, 30 (38), 5115-5118, Tetrahedron Lett., 1987, 28 (13), 1385-1388, Synthesis, 1985, (1), 45-48).

However, the prior art (1) requires an expensive starting material while the prior art (2) involves a very low reaction temperature of -78 ℃ to -40 ℃, so that neither is a favorable process for commercial-scale production.

DISCLOSURE OF INVENTION

The object of the present invention, in the above perspective, is to provide a production process by which a

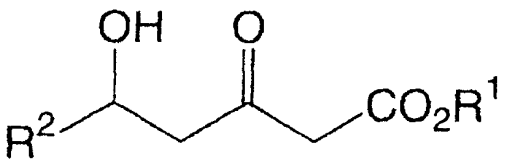
5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV), a useful pharmaceutical intermediate, can be prepared easily from a readily available, inexpensive starting material without using any extraordinary production equipment such as a very-low-temperature reactor:



(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group.

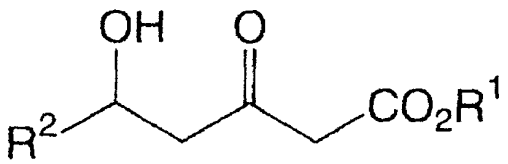
The inventors of the present invention made intensive investigations in view of the above state of the art and found that, starting with a readily available, inexpensive starting material, a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV) can be produced without using any special equipment such as a very-low-temperature reactor:



(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group.

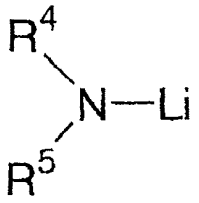
The present invention, therefore, relates to a process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

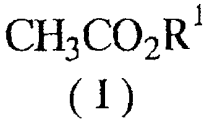
which comprises permitting a lithium amide of the following formula (III):



(III)

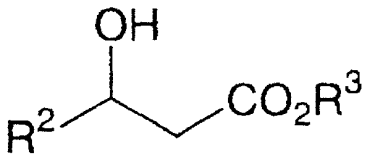
wherein R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms, and a silyl group

to act upon a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II) at a temperature not below -20 ℃:



(I)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:

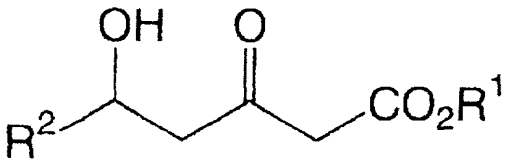


(II)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group;

R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 and R^3 may be joined to each other to form a ring.

The invention further relates to a process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



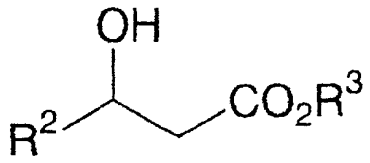
(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

which comprises treating a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II):

(I)

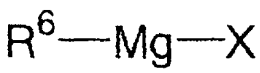
wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



(II)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 and R^3 may be joined to each other to form a ring

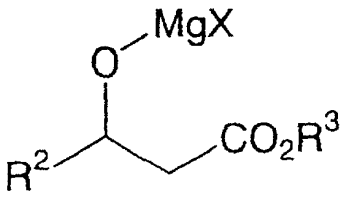
with a Grignard reagent of the following formula (V):



(V)

wherein R^6 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and X represents a halogen atom

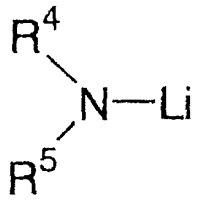
to prepare a mixture of a compound of the following formula (VI) and an acetic acid ester of the above formula (I):



(VI)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; R^2 and R^3 may be joined to each other to form a ring; and X represents a halogen atom,

and permitting a lithium amide of the following formula (III):

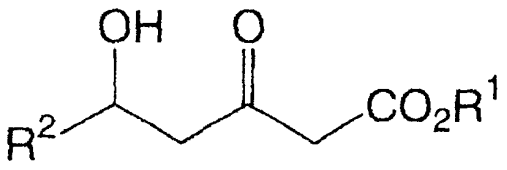


(III)

wherein R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms, and a silyl group,

to act upon the mixture at a temperature not below -20 ℃.

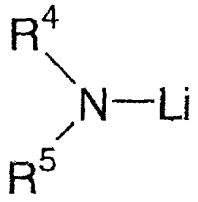
The present invention further relates to a process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

which comprises permitting a lithium amide of the following formula (III):



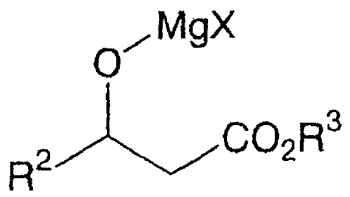
(III)

wherein R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

to act upon a mixture of an acetic acid ester of the following formula (I) and a compound of the following formula (VI) at a temperature not below -20 ℃:

$$CH_3CO_2R^1$$
(I)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



(VI)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; R^2 and R^3 may be joined to each other to form a ring; and X represents a halogen atom.

The present invention is now described in detail.

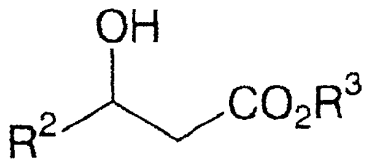
The acetic acid ester is represented by the general formula (I):

$$CH_3CO_2R^1$$
(I)

Here, R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms. As specific examples, there can be

mentioned methyl, ethyl, isopropyl, tert-butyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, benzyl, and p-nitrobenzyl, among others. Preferred is t-butyl.

The 3-hydroxypropionic acid derivative is represented by the general formula (II):



(II)

Here, R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group. As specific examples, there can be mentioned methyl, ethyl, isopropyl, tert-butyl, chloromethyl, bromomethyl, cyanomethyl, benzyloxymethyl, trityloxymethyl, tert-butyldiphenylsilyloxymethyl, dimethoxymethyl, 1,3-dithian-2-yl, 1,3-dithiolan-2-yl, vinyl, 2-phenylvinyl, 2-phenylethyl, 2-carbobenzyloxyaminoethyl, phenyl, naphthyl, p-methoxyphenyl, benzyl, p-nitrobenzyl, cyano, carboxy and tert-butoxycarbonyl, among others. Preferred are methyl, ethyl, isopropyl, tert-butyl, chloromethyl, cyanomethyl, benzyloxymethyl, trityloxymethyl, tert-butyldiphenylsilyloxymethyl, dimethoxymethyl, vinyl, 2-phenylethyl, phenyl, naphthyl, p-methoxyphenyl, benzyl and p-nitrobenzyl, among others. More preferred are chloromethyl, cyanomethyl and benzyloxymethyl.

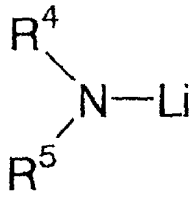
As the substituents on the alkyl, alkenyl, aryl and aralkyl groups each represented by the above R^2, there can be mentioned halogen, cyano, C_{7-19} aralkyloxy, C_{1-12} alkoxy, C_{6-12} aryl,

nitro, siloxy, N-protected amino, C_{1-12} alkylthio, C_{6-12} arylthio and C_{7-12} aralkylthio, among others. The number of substituents may be 0 to 3. The number of carbon atoms of said alkoxycarbonyl group in the above R^2 may for example be 2 to 13.

R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms. Specifically, methyl, ethyl, isopropyl, tert-butyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, benzyl, p-nitrobenzyl, etc. can be mentioned. Preferred is methyl or ethyl.

R^2 and R^3 may be joined to each other to form a ring; R^2 and R^3 specifically may jointly represent a methylene group, an ethylene group, a propylene group or the like, preferably a methylene group.

The lithium amide is represented by the general formula (III):



(III)

Here, R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms, and a silyl group. Specifically, there can be mentioned methyl, ethyl, isopropyl, tert-butyl, cyclohexyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, benzyl, p-nitrobenzyl, trimethylsilyl, triethylsilyl and phenyldimethylsilyl, among others. Preferred is isopropyl.

The Grignard reagent is represented by the general formula (V):

$$R^6—Mg—X$$

(V)

Here, R^6 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms. Specifically, there can be mentioned methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, benzyl and p-nitrobenzyl, among others. Preferred are methyl, ethyl, isopropyl, n-butyl, tert-butyl, etc. More preferred is tert-butyl. X represents a halogen atom. Preferred are chloro, bromo and iodo. More preferred is chloro.

The process for producing a 5-hydroxy-3-oxopentanoic acid derivative in accordance with the present invention is now described.

When a reaction involving an enolate such as an acetate-derived enolate is conducted at a non-very-low reaction temperature, for example not below -20℃, the self-condensation of the enolate proceeds predominantly to remarkably sacrifice the rate of conversion of the objective reaction. However, in the process developed by the present inventors, the self-condensation of the acetic enolate can be minimized so that the objective reaction can be carried out in high yield.

Thus, this reaction is carried out by adding a solution of a lithium amide dropwise to a mixed solution of an acetic acid ester and a 3-hydroxypropionic acid derivative. The acetic acid ester is not particularly restricted but includes, for example, methyl acetate, ethyl acetate, isopropyl acetate, t-butyl acetate, phenyl acetate and benzyl acetate. Preferred is t-butyl acetate. The amount of use of this acetic acid ester is preferably 1 to 5 molar equivalents, and more preferably 1.5 to 3 molar equivalents, based on the 3-hydroxypropionic acid derivative. The 3-hydroxypropionic acid derivative is not particularly restricted but includes methyl 3-

hydroxypropionate, ethyl 3-hydroxybutanoate, ethyl 3-hydroxypentanoate, ethyl 4-chloro-3-hydroxybutanoate, ethyl 4-bromo-3-hydroxybutanoate, 4-cyano-3-hydroxybutanoate, ethyl 4-benzyloxy-3-hydroxybutanoate, ethyl 4-trityloxy-3-hydroxybutanoate, ethyl 4-tert-butyldiphenyloxy-3-hydroxybutanoate, ethyl 3-cyano-3-hydroxypropionate, methyl 4,4-dimethoxy-3-hydroxybutanoate, ethyl 5-phenyl-3-hydroxyhexanoate, ethyl 5-carbobenzyloxyamino-3-hydroxyhexanoate, phenyl 3-phenyl-3-hydroxypropionate, methyl 3-naphthyl-3-hydroxypropionate, benzyl 4-phenyl-3-hydroxybutanoate, ethyl 4-p-nitrophenyl-3-hydroxybutanoate and 3-hydroxybutyrolactone, among others.

Furthermore, in accordance with the present invention, an optically active 3-hydroxypropionic acid derivative can be used as the starting material to give the corresponding objective compound without being sacrificed in optical purity. Therefore, more preferred are optically active ethyl 3-hydroxybutanoate, ethyl 4-chloro-3-hydroxybutanoate, ethyl 4-cyano-3-hydroxybutanoate, ethyl 4-benzyloxy-3-hydroxybutanoate, and 3-hydroxybutyrolactone, among others.

These optically active 3-hydroxypropionic acid derivatives can be easily prepared in accordance with the known production processes. For example, (3S)-4-chloro-3-hydroxybutyric acid ethyl ester can be produced by the process described in WO 98/35025; (3S)-4-cyano-3-hydroxybutyric acid ethyl ester can be produced by the process disclosed in Japanese Kohyo Publication Hei-7-500105; and (S)-3-hydroxybutyrolactone can be produced by the process described in Synthetic Communication 16, 183, 1986.

The lithium amide is not particularly restricted but includes lithium dimethylamide, lithium diethylamide, lithium diisopropylamide, lithium di-tert-butylamide, lithium dicyclohexylamide, lithium 2,2,6,6-tetramethylpiperidine, lithium diphenylamide, lithium dibenzylamide and lithium hexamethyldisilazide, among others. Preferred is lithium

diisopropylamide. These can be used each alone or two or more of them can be used in combination. The amount of use of the lithium amide relative to the 3-hydroxypropionic acid derivative is preferably 1 to 10 molar equivalents, more preferably 2 to 5 molar equivalents.

The yield of the objective compound can be increased by conducting this reaction in the presence of a magnesium halide. Thus, the reaction can be conducted with greater advantage by adding a solution of a lithium amide to a mixed solution containing the acetic acid ester, 3-hydroxypropionic acid derivative and magnesium halide. The magnesium halide is not particularly restricted but includes, for example, magnesium chloride, magnesium bromide and magnesium iodide. Preferred is magnesium chloride. The amount of use of the magnesium halide relative to the 3-hydroxypropionic acid derivative is preferably 0.5 to 10 molar equivalents, more preferably 1 to 5 molar equivalents.

Referring, further, to this reaction, the yield of the objective compound can be further improved by treating the 3-hydroxypropionic acid derivative with a Grignard reagent in advance to prepare the halomagnesium alkoxide compound and, then, conducting the reaction. In this case, the Grignard reagent is added dropwise to the 3-hydroxypropionic acid derivative to prepare the halomagnesium alkoxide compound and, after mixing the acetic acid ester, the lithium amide solution is added dropwise to carry out the reaction. As an alternative, the treatment with the Grignard reagent may be carried out in the presence of the acetic acid ester. Thus, the reaction can be conducted by adding the Grignard reagent to a mixed solution containing the acetic acid ester and 3-hydroxypropionic acid derivative and, then, adding the lithium amide solution dropwise to the reaction mixture. This Grignard reagent is not particularly restricted but includes for example methylmagnesium bromide, ethylmagnesium iodide, isopropylmagnesium chloride, n-butylmagnesium chloride and

tert-butylmagnesium chloride. Preferred is tert-butylmagnesium chloride. The amount of use of the Grignard reagent relative to the 3-hydroxypropionic acid derivative is preferably 0.5 to 5 molar equivalents. More preferred is 1 to 2 molar equivalents.

The solvent which can be used for this reaction may for example be an aprotic organic solvent. The organic solvent mentioned above includes hydrocarbon solvents such as benzene, toluene, n-hexane, cyclohexane, etc.; ether solvents such as diethyl ether, tetrahydrofuran, 1,4-dioxane, methyl t-butyl ether, dimethoxymethane, ethylene glycol dimethyl ether, etc.; halogen-containing solvents such as methylene chloride, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; and aprotic polar solvents such as dimethylpropyleneurea, N-methylpyrrolidone, hexamethylphosphoric triamide, etc., among others. These solvents may be used each alone or two or more of them may be used in a suitable combination. Preferred, among the above-mentioned solvents, are hydrocarbon solvents, such as benzene, toluene, n-hexane, cyclohexane, etc., and ether solvents, such as diethyl ether, tetrahydrofuran, 1,4-dioxane, methyl t-butyl ether, dimethoxymethane, ethylene glycol dimethyl ether and so on.

The reaction temperature for this reaction is preferably -20 ℃ to 80 ℃. More preferred is -10 ℃ to 40 ℃.

The aftertreatment of this reaction may be the routine aftertreatment for recovery of the reaction product from a reaction mixture. A typical procedure may comprise blending the reaction mixture at completion of the reaction with an aqueous solution of the common inorganic or organic acid, such as hydrochloric acid, sulfuric acid, nitric acid, acetic acid and citric acid, and carrying out an extraction with the common extractant such as ethyl acetate, diethyl ether, methylene chloride, toluene and hexane. From the extract obtained, the reaction solvent and extractant are distilled by heating under reduced pressure, for instance, whereby the objective product

can be isolated. The objective product thus obtained can be purified by the routine technique, such as crystallization, fractional distillation, column chromatography and/or the like to further enhance its purity.

BEST MODE FOR CARRYING OUT THE INVENTION

The following examples illustrate the present invention in further detail without defining its metes and bounds.

Example 1 Tert-butyl 6-benzyloxy-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 5.01 g (49.5 mmol) of diisopropylamine and 5 mL of tetrahydrofuran was added dropwise to 30 mL (45 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 ℃ and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 8.0 ml of tetrahydrofuran were dissolved 2.38 g (10 mmol) of ethyl 4-benzyloxy-3-hydroxybutyrate and 2.32 g (20 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 ℃. To this solution, the lithium diisopropylamide solution prepared above was added dropwise over 30 minutes, and the mixture was further stirred at 5 to 20 ℃ for 16 hours.

In a separate vessel, 35 mL of 3 N-hydrochloric acid was mixed with 30 mL of ethyl acetate under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 4:1) to give 1698 mg of tert-butyl 6-brenzyloxy-5-hydroxy-3-oxohexanoate (yellow oil) in 55% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz/ppm): 1.46 (9H, s), 2.75 (2H, d), 2.93 (1H, bs), 3.39 (2H, s), 3.47 (2H, m), 4.28 (1H, m), 4.55 (2H, s), 7.29-7.36 (5H, m)

^{13}C-NMR ($CDCl_3$, 400 MHz/ppm): 27.9, 46.1, 51.1, 66.6, 73.1, 73.3, 82.1, 127.7, 127.8, 128.4, 137.8, 166.1, 203.0

Example 2 Tert-butyl 6-benzyloxy-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 3.90 g (38.5 mmol) of diisopropylamine and 3 mL of tetrahydrofuran was added dropwise to 22.9 mL (35 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 ℃ and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 3.0 ml of tetrahydrofuran were dissolved 2.38 g (10 mmol) of ethyl 4-benzyloxy-3-hydroxybutyrate and 2.32 g (20 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 ℃. To this solution was added 5.7 g (10 mmol) of a solution of tert-butylmagnesium chloride in toluene/tetrahydrofuran (1:2.5 by weight) (1.75 mol/kg) dropwise over 10 minutes, and the mixture was further stirred at 5 ℃ for 50 minutes. To this, the lithium diisopropylamide solution prepared above was added dropwise over 30 minutes, and the mixture was further stirred at 5 to 20 ℃ for 16 hours.

In a separate vessel, 30 mL of 3 N-hydrochloric acid was mixed with 30 mL of ethyl acetate under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 4:1) to give 2420 mg of tert-butyl 6-brenzyloxy-5-hydroxy-3-oxohexanoate (red oil) in 79% yield.

Example 3 Tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 2.67 g (26.4 mmol) of diisopropylamine and 5 mL of tetrahydrofuran was added dropwise to 15 mL (24 mmol) of n-butyllithium/hexane (1.6 mol/L) with stirring at 5 ℃ and the mixture was stirred for 1 hour

to prepare a lithium diisopropylamide solution.

In 5.0 ml of tetrahydrofuran were dissolved 1.0 g (6.0 mmol) of ethyl (3S)-4-chloro-3-hydroxybutyrate and 2.78 g (24 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 ℃. To this the lithium diisopropylamide solution prepared above was added dropwise over 20 minutes, and the mixture was further stirred at 5 to 20 ℃ for 16 hours.

In a separate vessel, 6.31 g of concentrated hydrochloric acid, 20 g of water, and 20 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 4:1) to give 86 mg of tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate (colorless oil) in 6% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz/ppm): 1.48 (9H, s), 2.84 (1H, dd), 2.91 (1H, dd), 3.05 (1H, bs), 3.41 (2H, s), 3.55-3.64 (2H, m), 4.28-4.36 (1H, m)

Example 4 <u>Tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate</u>

Under argon gas, a solution composed of 10.0 g (99 mmol) of diisopropylamine and 20 mL of tetrahydrofuran was added dropwise to 56.3 mL (90 mmol) of n-butyllithium/hexane (1.6 mol/L) with stirring at 5 ℃ and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 10.0 ml of tetrahydrofuran were suspended 3.0 g (18.0 mmol) of ethyl (3S)-4-chloro-3-hydroxybutyrate, 5.22 g (45 mmol) of tert-butyl acetate and 6.86 g (72 mmol) of magnesium chloride, and the suspension was stirred in an argon atmosphere at 0 to 5 ℃. To this solution, the lithium diisopropylamide solution prepared above was added dropwise over 1 hour, and the

mixture was further stirred at 25 ℃ for 3 hours.

In a separate vessel, 21.7 g of concentrated hydrochloric acid, 30 g of water, and 30 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was washed with water twice and the solvent was distilled off under reduced pressure to give 5.62 g of a red oil containing tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate.

This oil was analyzed by high-performance liquid chromatography (column: Nacalai Tesque, Cosmosil 5CN-R (4.6 mm × 250 mm), eluent: water/acetonitrile = 9/1, flow rate: 1.0 ml/min, detection: 210 nm, column temperature: 40 ℃). The reaction yield was 65%.

Example 5 Tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 26.71 g (264 mmol) of diisopropylamine and 18.8 g of tetrahydrofuran was added dropwise to 150 mL (240 mmol) of n-butyllithium/hexane (1.6 mol/L) with stirring at 5 ℃ and the mixture was stirred to prepare a lithium diisopropylamide solution.

In 20 mL of tetrahydrofuran were dissolved 12.5 g (75 mmol) of ethyl (3S)-4-chloro-3-hydroxybutyrate and 17.4 g (150 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 ℃. To this solution was added 42.9 g (75 mmol) of a solution of tert-butylmagnesium chloride in toluene/tetrahydrofuran (1:2.5, by weight) (1.8 mol/kg) dropwise over 30 minutes, and the mixture was further stirred at 5 ℃ for 30 minutes. Then, the lithium diisopropylamide solution prepared above was added dropwise over 3 hours and the mixture was further stirred at 5 ℃ for 16 hours.

In a separate vessel, 60.38 g of concentrated hydrochloric acid, 31.3 g of water, and 50 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with water twice and the solvent was distilled

off under reduced pressure to give 22.0 g of a red oil containing tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate.

The reaction yields as analyzed by the method described in Example 3 was 78%.

Example 6 Tert-butyl (5S)-6-cyano-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 5.01 g (49.5 mmol) of diisopropylamine and 5 mL of tetrahydrofuran was added dropwise to 30 mL (45 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 ℃ and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 8.0 ml of tetrahydrofuran were suspended 1.57 g (10 mmol) of ethyl (3S)-4-cyano-3-hydroxybutyrate and 2.32 g (20 mmol) of tert-butyl acetate, and the suspension was stirred in an argon atmosphere at 0 to 5 ℃. To this solution, the lithium diisopropylamide solution prepared above was added dropwise over 30 minuets, and the mixture was further stirred at 5 to 20 ℃ for 16 hours.

In a separate vessel, 35 mL of 3 N-hydrochloric acid was mixed with 30 mL of ethyl acetate under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 3:1) to give 586 mg of tert-butyl (5S)-6-cyano-5-hydroxy-3-oxohexanoate (red oil) in 26% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz/ppm): 1.48 (9H, 2), 2.61 (2H, m), 2.90 (2H, m), 3.42 (3H, s), 4.41 (1H, m)

^{13}C-NMR ($CDCl_3$, 400 MHz/ppm): 25.0, 28.0, 48.0, 50.9, 63.6, 82.8, 117.0, 166.0, 202.8

Example 7 Tert-butyl (5S)-6-cyano-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 5.01 g (49.5 mmol)

of diisopropylamine and 5 mL of tetrahydrofuran was added dropwise to 30 mL (45 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 ℃ and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 8.0 ml of tetrahydrofuran were suspended 1.57 g (10 mmol) of ethyl (3S)-4-cyano-3-hydroxybutyrate, 2.32 g (20 mmol) of tert-butyl acetate and 2.86 g (30 mmol) of magnesium chloride, and the suspension was stirred in an argon atmosphere at 0 to 5 ℃. To this solution, the lithium diisopropylamide solution prepared above was added dropwise over 30 minutes, and the mixture was further stirred at 5 to 20 ℃ for 16 hours.

In a separate vessel, 35 mL of 3 N-hydrochloric acid was mixed with 30 mL of ethyl acetate under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 3:1) to give 1041 mg of tert-butyl (5S)-6-cyano-5-hydroxy-3-oxohexanoate (red oil) in 46% yield.

Example 8 Tert-butyl (5S)-6-cyano-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 3.90 g (38.5 mmol) of diisopropylamine and 3 mL of tetrahydrofuran was added dropwise to 22.9 mL (35 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 ℃ and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 3.0 mL of tetrahydrofuran were dissolved 1.57 g (10 mmol) of ethyl (3S)-4-cyano-3-hydroxybutyrate and 2.32 g (20 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 ℃. To this solution was added 5.7 g (10 mmol) of a solution of tert-butylmagnesium chloride in toluene/tetrahydrofuran (1:2.5, by weight) (1.75 mol/kg) dropwise over 10 minutes, and the mixture was further stirred

at 5 ℃ for 50 minutes. Then, the lithium diisopropylamide solution prepared above was added dropwise over 30 minutes and the mixture was further stirred at 5 to 20 ℃ for 16 hours.

In a separate vessel, 30 mL of 3 N-hydrochloric acid and 30 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 3:1) to give 1302 mg of tert-butyl (5S)-6-cyano-5-hydroxy-3-oxohexanoate (red oil) in 57% yield.

Example 9 Tert-butyl (5S)-5,6-dihydroxy-3-oxohexanoate

Under argon gas, a solution composed of 5.01 g (49.5 mmol) of diisopropylamine and 5 mL of tetrahydrofuran was added dropwise to 30 mL (45 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 ℃ and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 8.0 ml of tetrahydrofuran were suspended 1.02 g (10 mmol) of (3S)-3-hydroxybutyrolactone and 2.32 g (20 mmol) of tert-butyl acetate, and the suspension was stirred in an argon atmosphere at 0 to 5 ℃. To this solution, the above lithium diisopropylamide solution was added dropwise over 30 minuets, and the mixture was further stirred at 5 to 20 ℃ for 16 hours.

In a separate vessel, 35 mL of 3 N-hydrochloric acid and 30 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column

chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 2:1) to give 124 mg of tert-butyl (5S)-5,6-dihydroxy-3-oxohexanoate (yellow oil) in 6% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz/ppm): 1.48 (9H, s), 2.668-2.83 (2H, m), 3.0-3.8 (2H, bs), 3.42 (2H, s), 4.02-4.17 (2H, m), 4.40 (1H, m)

^{13}C-NMR ($CDCl_3$, 400 MHz/ppm): 27.8, 45.7, 51.0, 65.6, 68.0, 82.3, 166.4, 203.4

Example 10 Tert-butyl (5S)-5,6-dihydroxy-3-oxohexanoate

Under argon gas, a solution composed of 3.90 g (38.5 mmol) of diisopropylamine and 3 mL of tetrahydrofuran was added dropwise to 22.9 mL (35 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 ℃ and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 3.0 mL of tetrahydrofuran were dissolved 1.02 g (10 mmol) of (3S)-3-hydroxybutyrolactone and 2.32 g (20 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 ℃. To this solution was added 5.7 g (10 mmol) of a solution of tert-butylmagnesium chloride in toluene/tetrahydrofuran (1:2.5, by weight) (1.75 mol/kg) dropwise over 10 minutes, and the mixture was further stirred at 5 ℃ for 50 minutes. Then, the lithium diisopropylamide solution prepared above was added dropwise over 30 minutes and the mixture was further stirred at 5 to 20 ℃ for 16 hours.

In a separate vessel, 30 mL of 3 N-hydrochloric acid and 30 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 2:1) to give 980 mg of tert-butyl (5S)-5,6-dihydroxy-3-

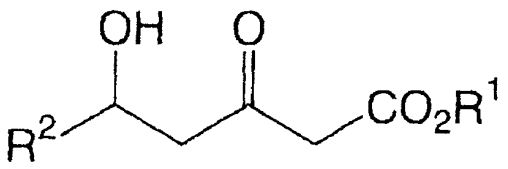
oxohexanoate (red oil) in 48% yield.

INDUSTRIAL APPLICABILITY

The present invention, constituted as described above, enables the production of 5-hydroxy-3-oxopentanoic acid derivatives, which are of use as pharmaceutical intermediates, particularly intermediates of HMG-CoA rductase inhibitors, from inexpensive, readily available starting compounds at a non-very-low temperature.

CLAIMS

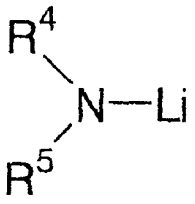
1. A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

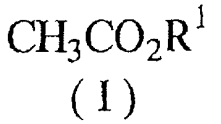
which comprises permitting a lithium amide of the following formula (III):



(III)

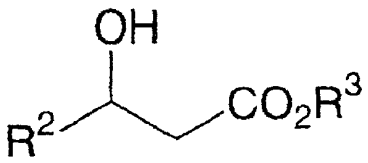
wherein R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

to act upon a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II) at a temperature not below -20 ℃:



(I)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



(II)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 and R^3 may be joined to each other to form a ring.

2. The process according to Claim 1

wherein, referring to the lithium amide, R^4 and R^5 each represents an isopropyl group.

3. The process according to Claim 1 or 2

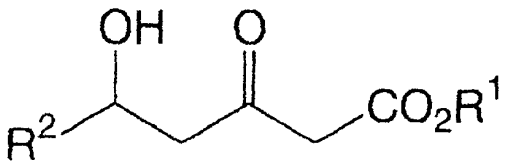
wherein, referring to the acetic acid ester, R^1

represents a tert-butyl group.

4. The process according to Claim 1, 2 or 3 wherein a magnesium halide is added in permitting the lithium amide to act.

5. The process according to Claim 4 wherein magnesium chloride is used as the magnesium halide.

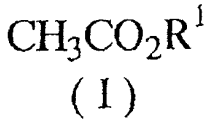
6. A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



(IV)

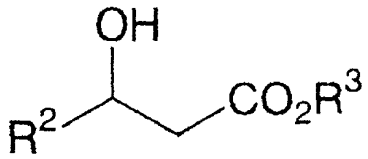
wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

which comprises treating a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II):



(I)

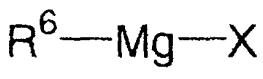
wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



(II)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 and R^3 may be joined to each other to form a ring,

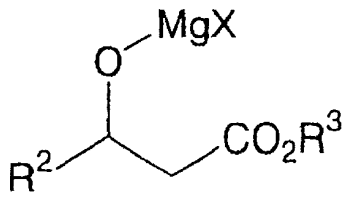
with a Grignard reagent of the following formula (V):



(V)

wherein R^6 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and X represents halogen,

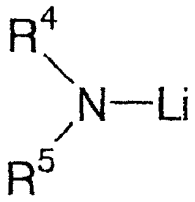
to prepare a mixture of a compound of the following formula (VI) and an acetic acid ester of the above formula (I):



(VI)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; R^2 and R^3 may be joined to each other to form a ring; and X represents a halogen atom,

and permitting a lithium amide of the following formula (III):



(III)

wherein R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group

to act upon the mixture at a temperature not below -20 ℃.

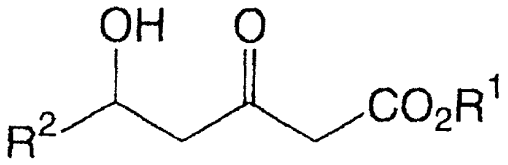
7. The process according to Claim 6

wherein, referring to the lithium amide, R^4 and R^5 each is an isopropyl group.

8. The process according to Claim 6 or 7 wherein, referring to the acetic acid ester, R^1 represents a tert-butyl group.

9. The process according to Claim 6, 7 or 8 wherein, referring to the Grignard reagent, R^6 represents a tert-butyl group and X represents a chlorine atom.

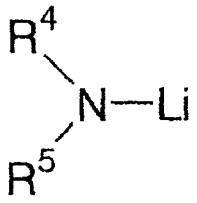
10. A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



(IV)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

which comprises permitting a lithium amide of the following formula (III):



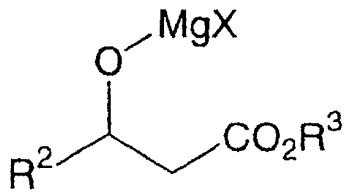
(III)

wherein R^4 and R^5 may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

to act upon a mixture of an acetic acid ester of the following formula (I) and a compound of the following formula (VI) at a temperature not below -20 ℃:

(I)

wherein R^1 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



(VI)

wherein R^2 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent,

a cyano group, a carboxyl group and an alkoxycarbonyl group; R^3 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; R^2 and R^3 may be joined to each other to form a ring; and X represents a halogen atom.

11. The process according to Claim 10 wherein, referring to the lithium amide, R^4 and R^5 each represents an isopropyl group.

12. The process according to Claim 10 or 11 wherein, referring to the acetic acid ester, R^1 represents a tert-butyl group.

13. The process according to Claim 10, 11 or 12 wherein, referring to the compound (VI), X represents a chlorine atom.

14. The process according to any of Claims 1 to 13 wherein R^3 is a methyl group or an ethyl group.

15. The process according to any of Claims 1 to 14 wherein R^2 is a chloromethyl group, a cyanomethyl group or a benzyloxymethyl group.

16. The process according to any of Claims 1 to 13 wherein R^2 and R^3 are joined to each other to form a methylene group.

17. The process according to any of Claims 1 to 16 wherein the compound (II) or (VI) is optically active.

ABSTRACT

This invention provides a process for producing a 5-hydroxy-3-oxopentanoic acid, a useful pharmaceutical intermediate, easily from a readily available, inexpensive starting material without using any extraordinary production equipment such as a very-low-temperature reactor.

Thus, this invention provides a process for producing a 5-hydroxy-3-oxopentanoic acid

which comprises permitting a lithium amide to act upon a mixture of an acetic acid ester and a 3-hydroxypropionic acid derivative at not below -20 ℃.

Further, this invention also provides a process for producing a 5-hydroxy-3-oxopentanoic acid

which comprises treating a mixture of an acetic acid ester and a 3-hydroxypropionic acid derivative with a Grignard reagent to prepare a mixture of a compound and an acetic acid ester of the above formula (I),

and permitting a lithium amide to act upon the mixture at a temperature not below -20 ℃.

05 APR 2001

09/762215

DECLARATION FOR PATENT APPLICATION

1581/00240

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled.

Processes for the Preparation of 5-Hydroxy-3-Oxopentanoic Acid Derivatives

the specification of which (check one)

[ ] is attached hereto

[XX] was filed on June 2, 2000, as United States Patent Application Serial No or PCT International Application Number PCT/JP00/03574, and was amended on _____ 19__ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 CFR § 1.56(a)

Prior Foreign Application(s) I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

			Priority Claimed	
11/158033	Japan	4/June/1999	[XX]	[ ]
(Application No.)	(Country)	(Day/Month/Year Filed)	YES	NO
2000/23804	Japan	1/February/2000	[XX]	[ ]
(Application No.)	(Country)	(Day/Month/Year Filed)	YES	NO
_____	_____	_____	[ ]	[ ]
(Application No.)	(Country)	(Day/Month/Year Filed)	YES	NO

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date
_____	_____
_____	_____

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below or 34 U.S.C § 365(c) of any PCT International Application designating the United States of America listed below, and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application or PCT application in the manner provided by 35 U.S.C. § 112, first paragraph, I acknowledge the duty to disclose material information as defined in 37 CFR § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

_____	_____	_____
(U.S. or PCT Application Serial No.)	(U.S. or PCT Filing Date)	(Status - patented, pending, abandoned)
_____	_____	_____
(U.S or PCT Application Serial No)	(U.S or PCT Filing Date)	(Status - patented, pending, abandoned)

I hereby appoint the following registered practitioners. George Vande Sande, Registration No. 17,276, Burton A. Amernick, Registration No. 24,852; Richard Wiener, Registration No. 18,741; Townsend M. Belser, Jr., Registration No. 22,956; Morris Liss, Registration No 24,510; George R. Pettit, Registration No. 27,369; Elzbieta Chlopecka, Registration No. 32,767; William E Curry, Registration No 43,572, David W. Ward, Registration No 45,198, and John A. Evans, Ph.D., Registration No 44,100, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Residence Address _____
Citizenship _____
Post Office Address _____

Full name of fourth joint inventor (if any) _____

Inventor's Signature _____ Date _____
Residence Address _____
Citizenship _____
Post Office Address _____

Full name of fifth joint inventor (if any) _____

Inventor's Signature _____ Date _____
Residence Address _____
Citizenship _____
Post Office Address _____

Full name of sixth joint inventor (if any) _____

Inventor's Signature _____ Date _____
Residence Address _____
Citizenship _____
Post Office Address _____

Full name of seventh joint inventor (if any) _____

Inventor's Signature _____ Date _____
Residence Address _____
Citizenship _____
Post Office Address _____

Full name of eighth joint inventor (if any) _____

Inventor's Signature _____ Date _____
Residence Address _____
Citizenship _____
Post Office Address _____